REMARKS/ARGUMENTS

The Pending Claims

Claims 1-37 currently are pending. Claims 1-16 and 30-37 have been withdrawn in response to a restriction requirement. As such, claims 17-29 are subject to examination.

Amendments to the Claims

The claims have been amended to point out more particularly and claim more distinctly the invention. Specifically, claim 17 has been amended to recite a method of immunizing an animal including the step of administering an isolated nucleic acid capable of producing an infectious *attenuated* Kunjin virus. Support for this amendment can be found throughout the specification, for example, at page 4, line 25, through page 5, line 2.

Accordingly, no new matter has been added by way of these amendments.

The Office Action

Claims 17, 18, and 25 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. Claims 17-29 have been rejected under 35 U.S.C. § 102(a) as allegedly anticipated by Hall et al., *PNAS*, 100: 10460-10464 (2003) ("Hall et al."). Claims 17-23, 26, and 28 have been rejected under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. Patent No. 6,893,866 (Westaway et al.) ("the '866 patent"). Claims 17-24 and 26-29 have been rejected under 35 U.S.C. § 103(a) as allegedly obvious over Anraku et al., *Journal of Virology*, 76: 3791-3799 (2002) ("Anraku et al."). Claims 17-29 have been provisionally rejected for obviousness-type double patenting as allegedly unpatentable over claims 29-31 of copending U.S. Patent Application No. 10/559,146 ("the '146 application"). Reconsideration of these rejections is respectfully requested in view of the claim amendments and remarks herein.

Discussion of Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 17, 18, and 25 have been rejected as allegedly failing to comply with the enablement requirement.

The Examiner contends that the specification does not reasonably provide enablement for the method of immunizing an animal comprising administering an isolated nucleic acid capable of producing an *infectious* Kunjin virus. Specifically, the Examiner contends that the administration of infectious Kunjin virus may cause infection and possibly death in an animal. Therefore, the Examiner alleges that it would be necessary for one of ordinary skill in the art to attenuate the virus for the purposes of immunization.

Applicants wish to point out that one of ordinary skill in the art would recognize that Kunjin virus is a naturally occurring, substantially attenuated strain of West Nile virus that rarely produces significant disease in humans (see, for example, paragraph 0003). In mouse models, peripheral inoculation of mice with Kunjin virus only causes disease in baby mice (less than 21 days old), and does not produce disease symptoms in adult mice. The vast majority of Kunjin virus infections in humans are benign, and infections are never fatal. In fact, it is now well established in the art that it was not Kunjin virus that caused the death of humans as reported by Briese et al., *The Lancet*, 354: 1261-1262 (1999), but rather NY99 strain of West Nile virus.

The Examiner acknowledges that the specification enables a method of inducing an immune response in an animal comprising administering an isolated nucleic acid capable of producing an *attenuated* Kunjin virus. Solely in an effort to advance prosecution of the instant application, and not in acquiescence of the rejection, claim 17 has been amended to recite a method of immunizing an animal including the step of administering an isolated nucleic acid capable of producing an infectious *attenuated* Kunjin virus.

The Examiner states that the specification of the instant application is enabled for a method of vaccinating mice against the West Nile NY99 strain. However, the Examiner alleges that the specification is not enabled for a method of immunizing *any* animal against *any* flavivirus, as recited in the pending claims.

It is well known in the art that evaluation of a potential immunotherapeutic composition or vaccine in mice is a fundamental first step in the development of vaccines for human use. Specifically, assessment of the safety and efficacy of flavivirus vaccines in mice is well recognized in the art as the first step of preclinical evaluation. Moreover, there are many studies showing a correlation between the efficacy of flavivirus vaccines in mice and in

humans. Historically, this has been clearly demonstrated for the development of Yellow fever, Japanese encephalitis, and tick-borne encephalitis vaccines, where efficacy in preclinical studies in mice correlated well with successful clinical trials in human volunteers (see, for example, Guirakhoo et al., *Virology*, 257: 363-372 (1999), and Monath et al., *Vaccine*, 20: 1004-1018 (2002), submitted herewith).

In addition, the National Institute of Allergy and Infectious Diseases (NIAID) antiviral evaluation service specifically utilizes mouse and hamster animal models of human viral infection in relation to West Nile virus and Yellow fever virus (see, for example, Table 1 of Greenstone et al., *Antiviral Research*, 78: 51-59 (2008), submitted herewith). Moreover, rodent models of human viral infection have been used to support Investigational New Drug filings for clinical development before the Food and Drug Administration, further demonstrating that rodents are an accepted and well established animal model for human disease in flavivirus vaccine development.

Cross-protection between certain members of the Japanese encephalitis subgroup of flaviviruses has been published (see, for example, Tesh et al., *Emerging Infectious Diseases*, 8: 245-251 (2002), submitted herewith). In addition, it has been observed through unpublished *in vitro* experiments by the Applicants that sera from humans and horses naturally infected with Kunjin virus neutralize the virulent North American strain of West Nile virus. This experimental observation clearly supports the assertion that a Kunjin virus-based immunotherapeutic composition will likely generate protective immunity against at least another flavivirus in humans. Therefore, Applicants submit that there is a reasonable expectation that administration of an isolated nucleic acid capable of producing an infectious attenuated Kunjin virus will elicit a protective immune response to at least another flavivirus, as recited in the pending claims.

The Examiner contends that claim 25 fails to comply with the enablement requirement because the West Nile virus strain NY99 must be known and readily available to the public.

The West Nile virus NY99 strain (isolate 4132) used in the context of the present invention was isolated from a crow in New York in 1999 and it is genetically identical to the prototype New York isolate described in Lanciotti et al., *Science*, 286: 2333-2337 (1999)

(submitted herewith). The West Nile virus NY99 strain (isolate 4132) disclosed in the instant application is available to the public from the Division of Vector-Borne Infectious Diseases, Centers for Disease Control, 3150 Rampart Road, Fort Collins, CO 80521 (see paragraph 0108 of the specification). In addition, West Nile virus NY99 strain is also available under Catalogue No. NR-677 from the Biodefense and Emerging Infections Research Resources Repository, BEI Resources, 10801 University Boulevard, Manassas, VA 20108. Therefore, Applicants submit that West Nile virus strain NY99 is known and readily available to the public.

In view of the foregoing, Applicants submit that one of ordinary skill in the art would be able to practice the present invention, as recited in the pending claims, in view of the working examples provided in the instant application and the state of the prior art. Accordingly, the rejection under Section 112, first paragraph, should be withdrawn.

Discussion of Rejection Under 35 U.S.C. § 102(a)

Claims 17-29 have been rejected as allegedly anticipated by Hall et al. Hall et al. was published less than one year before the earliest effective U.S. filing date for the pending claims. Accordingly, Hall et al. qualifies as prior art only if the reference was published "by another." See, e.g., 35 U.S.C. § 102(a). Applicants submit herewith a Declaration under 37 C.F.R. § 1.132, executed by Alexander Khromykh and Roy Hall, stating that Hall et al. describes the inventors' own work. Accordingly, Hall et al. is not prior art to the pending claims under 35 U.S.C. § 102(a) and cannot, therefore, be cited as a basis for rejection of the present application. See *In re Katz,* 687 F.2d 450, 215 U.S.P.Q. 14 (C.C.P.A. 1982).

In view of the foregoing, the section 102(a) rejection is improper and should be withdrawn.

Discussion of Rejection Under 35 U.S.C. § 102(e)

Claims 17-23, 26, and 28 have been rejected as allegedly anticipated by the '866 patent. The Examiner contends that the '866 patent discloses a method for immunizing an animal comprising administering an attenuated Kunjin virus replicon comprising a nucleotide encoding HCV proteins belonging to the flavivirus family.

Claims 17-23, 26, and 28 are directed to a method of immunizing an animal which includes the step of administering an isolated nucleic acid capable of producing an infectious attenuated Kunjin virus. In order to produce an infectious Kunjin virus, as recited in the pending claims, the isolated nucleic acid must have the ability to produce a full length Kunjin virus RNA genome that can be packaged into virions, released from the cell, and enter other cells, resulting in cell-to-cell spread of the virus through multiple-rounds of infection.

The '866 patent describes the construction of three Kunjin virus replicons which encode HCV proteins, namely C20DX/hcvCORE160/2Arep, C20DX/hcvCORE191/2Arep, and C20DX/hcvNS3/2Arep (see column 27 and FIG 10B). The CD20DX/2Arep nucleic acid constructs disclosed in the '866 patent lack the coding sequence for a flavivirus core protein and the flavivirus prM and E proteins, which are the necessary structural proteins that assemble and form an infectious Kunjin virus particle. Therefore, the C20DX-2Arep nucleic acid constructs disclosed in the '866 patent require the expression of flaviviral structural core, prM, and E proteins from a separate nucleic acid construct, namely a Semliki Forest Virus (which is unrelated to flaviviruses) replicon, in order for assembly of Kunjin virus replicon RNAs into Kunjin virus-like particles.

In view of the foregoing, the '866 patent discloses isolated nucleic acid constructs which encode HCV proteins and are incapable of producing an infectious Kunjin virus particle. Moreover, the '866 patent does not disclose or suggest administration of an isolated nucleic acid capable of producing an infectious attenuated Kunjin virus to elicit a protective immune response to at least another flavivirus. The sole demonstration of an immunogenic response in the '866 patent is as a result of administration of Kunjin virus replicon virus-like particles (VLPs) containing packaged C20DX/GFP/2Arep RNA in which a humoral immune response was detected (see Example 8).

Accordingly, the '866 patent does not disclose or suggest a method of immunizing an animal including the step of administering an isolated nucleic acid capable of producing an infectious Kunjin virus to the animal to thereby elicit a protective immune response to at least another flavivirus, as recited in the pending claims, and the anticipation rejection should be withdrawn.

Discussion of Rejection Under 35 U.S.C. § 103(a)

Claims 17-24 and 26-29 have been rejected as allegedly obvious over Anraku et al. The Examiner alleges that Anraku et al. teaches a method of immunizing an animal comprising administering a nucleic acid encoding an attenuated Kunjin virus genome comprising nucleic acids encoding foreign heterologous epitopes. The Examiner acknowledges that Anraku et al. does not teach generating an immune response to at least another flavivirus by administration of Kunjin virus replicons. However, the Examiner contends that Anraku et al. teaches that Kunjin virus replicons have been shown to be effective vaccine vectors for induction of a protective immune response against HIV and other viral pathogens. Therefore, the Examiner alleges that it would have been obvious to incorporate immunogenic epitopes of other flaviviruses, such as HCV or West Nile virus, in the Kunjin virus replicons to generate an immune response against infection with HCV or West Nile virus.

Claims 17-24 and 26-29 are directed to a method of immunizing an animal including the step of administering an isolated nucleic acid capable of producing an *infectious* attenuated Kunjin virus to elicit a protective immune response to at least another flavivirus. As discussed above, in order to produce an infectious Kunjin virus, the isolated nucleic acid must have the ability to produce a full length Kunjin virus RNA genome. As such, the present invention, as recited in the pending claims, essentially utilizes a genomic copy of one flavivirus (i.e., Kunjin virus) to immunize against at least another flavivirus. Applicants wish to point out that the present invention provides the first ever report of protective immunization by administration of a DNA copy of a flavivirus genome and, more particularly, immunization by a non-pathogenic flavivirus genome (i.e., Kunjin) against a far more virulent and pathogenic flavivirus, namely the NY99 strain of West Nile virus.

In contrast to the claimed invention, Anraku et al. discloses the use of Kunjin virus replicons as vaccine vectors to deliver foreign, heterologous immunogens (i.e., Kunjin virus is *not* the immunogen). Moreover, the Kunjin virus replicons disclosed in Anraku et al. do not have the ability to produce an infectious Kunjin virus, but rather require the use of an unrelated Semliki Forest virus for the production of Kunjin structural proteins. Specifically, Anraku et al. teaches that the heterologous nature of the Kunjin replicon packaging system,

which employs a replicon RNA-based vector from a totally unrelated virus for the expression of Kunjin structural proteins, makes the Kunjin virus-like particle preparations absolutely safe and free of any infectious recombinant viral material (see page 3798, first paragraph). In addition, Anraku et al. teaches that the disclosed Kunjin replicon packaging system eliminates any potential problems associated with the contamination of virus-like particles with infectious recombinant material (see page 3791, second paragraph).

Accordingly, Anraku et al. does not disclose or suggest the use of an isolated nucleic acid capable of producing an infectious virus, much less an infectious attenuated Kunjin virus, as recited in the pending claims. In fact, Anraku et al. teaches that it is advantageous to use a Kunjin virus replicon packaging system that *prevents* the production of infectious viral material. Therefore, Applicants submit that one of ordinary skill in the art would not modify the Kunjin virus packaging system disclosed in Anraku et al. to produce an infectious Kunjin virus because Anraku et al. explicitly teaches away from the use of infectious viral material.

The Examiner alleges that it would have been obvious to incorporate immunogenic epitopes of other flaviviruses, such as HCV or West Nile virus, in the Kunjin virus replicons to generate an immune response against infection with HCV or West Nile virus. As pointed out by the Examiner, Anraku et al. teaches a Kunjin virus-based vaccine vector that is useful for the delivery of foreign immunogens, and does not suggest replacing the foreign immunogen with the Kunjin virus itself. Accordingly, Anraku et al. does not disclose or suggest the use of Kunjin virus to elicit a protective immune response to at least another flavivirus, as recited in the claims in issue.

In view of the foregoing, the subject matter of claims 17-24 and 26-29 would not have been obvious in view of Anraku et al., and the obviousness rejection should be withdrawn.

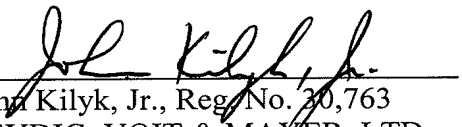
Obviousness-Type Double Patenting Rejection

Claims 17-29 have been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 29-31 of copending U.S. Patent Application No. 10/559,146 ("the '146 application"). Applicants will consider filing a terminal disclaimer upon an indication that the rejection is no longer provisional.

Conclusion

Applicants respectfully submit that the patent application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,



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